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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,073	03/07/2006	Philip N. Bryan	4115181	2283

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INTELLECTUAL PROPERTY / TECHNOLOGY LAW
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EXAMINER	
MOORE, WILLIAM W	
ART UNIT	PAPER NUMBER
1656	
MAIL DATE	DELIVERY MODE
12/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,073	BRYAN, PHILIP N.	
	Examiner	Art Unit	
	WILLIAM W. MOORE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2008 and 13 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *18-45 and 50-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11-17 and 46-49* is/are rejected.

7)☒ Claim(s) *9 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20081013*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Applicant's Amendments to claims 1-4, 7, 9-13, 15, 20-22, 25, 37, 38, 44-50, and 53-59, as well as the amendments to paragraphs at pages 6, 20-21, and 25-27 of the specification filed on 12 August 2008, have been entered. Claims 1-61 remain in the application, of which claims 18-45 and 50-61 remain withdrawn from consideration pursuant to Applicant's election of the invention of Group 1 in the reply filed 18 January 2008, which invention includes methods and products comprising subtilisin species S189, S190, S196, S197, S198, S199, or S201.

The amendments overcome the objections of record to specification and claims for informalities and, together with Applicant's submission of a revised sequence listing in printed and computer-readable form, overcome the objections of record of the specification for an apparent lack of essential material and all but one of the bases for the objection of record for lack of sequence rules compliance. As such, Applicant's submissions are considered to be a *bona fide* effort to bring the disclosure into compliance with 37 CFR 1.821. The remaining basis for objection, concerning claim 10, is restated below. Together with Applicant's arguments in the accompanying Remarks, the claim amendments overcome the rejection of record of claims herein under the second paragraph of 35 U.S.C. § 112, which rejection is WITHDRAWN. The amendments to claims 3, 7, and 13 necessitate the statement, however, of a new ground of rejection which appears below.

Objection to the Specification: Lack of Sequence Rules Compliance

The application contains a remaining sequence disclosure, the nonapeptide recited in claim 10, encompassed by the definition for amino acid sequences set forth in 37 CFR 1.821(a)(2) lacking a sequence identifier. Stating a sequence identifier elsewhere in the specification does not release claim 10 from the requirement that each reference to peptides larger than tetramers in the specification or claims must be accompanied by a sequence identifier stating "SEQ ID NO:N", and in the case of claim 10 must clearly be "SEQ ID NO:7". Appropriate correction is required in responding to this communication.

Information Disclosure Statement

Applicant's Supplemental IDS filed, in duplicate, on 13 October 2008 and citing Hedstrom, 2002, Appendix B of Applicant's Remarks filed the same date, is hereby acknowledged. No copy of Strausberg et al., 1995, cited in the IDS, was submitted and this citation is lined-through on the executed Form PTO-1449 accompanying this communication. Applicant's Remarks, at

page 23, supply sufficient information for citing Strausberg et al., 2005, Applicant's Appendix A, on the accompanying Form PTO-892.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 7, and 13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 7, and 13 are each indefinite because the claim amendments filed 12 August 2008 produce the recitation in each, "prodomain is modified to bind subtilisin or a variant thereof with increased affinity as compared to an unmodified prodomain protein", yet no particular subtilisin is identified in any of claims 3, 7, or 13 that would permit the artisan and the public seeking to determine the metes and bounds of the claimed subject matter to differentiate any particular subtilisin from a "variant thereof". Equally, claims 3, 7, and 13 are each indefinite because a prodomain protein further comprising one of more amino acid substitutions according to the preceding recitations in each claim cannot be distinguished by the artisan and the public seeking to determine the metes and bounds of the claimed subject matter from a "compar[ison] prodomain protein with no substitutions" unless the structure of a prodomain protein with no substitutions is identified in the recitations of the claims. Since a variant prodomain according to the claims must have an increased binding affinity to a generic subtilisin, or to a generic variant of the generic subtilisin, the absence of any structure defining a starting point for determining what is, and what is not, a prodomain with no substitutions leaves the scope of the claims 3, 7 and 13 indeterminate and indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 USC § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 46, and 47 remain rejected for reasons of record under 35 USC § 102(e) as being anticipated by Van Rooijen et al., US 2003/0166162, of record.

Applicant's arguments at pages 20-22 of the Remarks filed 12 August 2008 have been fully considered but they are not persuasive. Applicant identifies no amendment of claims 46 and 47 that might avoid the disclosure of Van Rooijen et al. but points to an amendment of claim 1 that introduces the term "high affinity" as well as to a "definition" at page 18 of the specification of "binding with high affinity" that, were it to be stated verbatim in a claim, would be indefinite because it includes three different ranges for dissociation constants. It is noted that only one claim pending in the application, the non-elected claim 24, states an unambiguous affinity but neither claim 24, nor claims 19 and 21 from which it depends, indicate any particular structures conferring the stated degree of affinity, deficiency suffered by claim 1 as well. Since Applicant's purported definition is ambiguous, claim 1 is construed to state a relative term for the encoded fusion protein as a whole, i.e., that a fusion protein comprising both a generic prodomain and a generic protein of interest exhibits a higher binding affinity to a generic protease, and its further generic variants, than would a fusion protein comprising a "protein of interest" and a second fusion partner not a prodomain protein. As such, the disclosure of Van Rooijen et al of the preparation of polynucleotides encoding fusion polypeptides comprising any one of several modified chymosin prodomains fused directly to the amino terminus of any one of several desired, carboxyl-proximal, polypeptide fusion partners wherein a modified prodomain present in the recombinantly expressed fusion polypeptides is disclosed to have an improved affinity for chymosin as shown by increased yields of cleaved fusion partner achieved, relative to that achieved with an unmodified chymosin prodomain, has "high affinity" for chymosin relative to a non-prodomain fusion partner as well as "high affinity" relative to a fusion partner that is an unmodified chymosin prodomain. The rejection of record of record is therefore maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 USC § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 5, 7, 8, 11, 12, 13, 14, 17, and 48 remain rejected for reasons of record under 35 USC § 103(a) as being unpatentable over Van Rooijen et al. as applied to claims 1, 46, and 47 above, in view of Grøn et al., 1996, of record.

Applicant's arguments at pages 22 and 23 of the Remarks filed 12 August 2008 have been fully considered but they are not persuasive. Applicant again points to the amendment of claim

1 that introduces the term "high affinity" and discusses Table 3 of Grøn et al., 1996, relied upon in this rejection of record. Applicant suggests that catalytic efficiency does not involve affinity, and, while Applicant acknowledges that the Michaelis constant comprises "a measure of the affinity of a substrate for an enzyme", the denominator K_m, Applicant believes that efficiency of catalysis implicates only the most transient binding of a subtilisin to a modified prodomain taught by Grøn et al. Because Van Rooijen et al. teach modifications of a chymosin prodomain that provides a higher affinity for chymosin recognition in a fusion polypeptide comprising a modified protease prodomain and a hormone than in a fusion polypeptide comprising a hormone and an unmodified protease prodomain, it is considered to be properly combined with the teaching of Grøn et al. of improving the affinity of a subtilisin modified to better accept the S4 amino acid of a subtilisin prodomain's carboxyl terminal region introduced in modified peptide substrates that represent the P4-P3-P2-P1 peptide of the "corresponding" unmodified prodomain, using nucleic acid constructs encoding the modified subtilisin and encoding the modified subtilisin prodomain, wherein the P4 position is modified by introducing phenylalanine, and to meet the limitations of claims 2, 5, 7, 8, 11, 12, 13, 14, 17, and 48 herein where hormones are among the fusion partners of claim 11. The rejection of record is therefore sustained.

Claims 4, 6, 15, and 16 remain rejected for reasons of record, and claim 49 is now rejected, under 35 USC § 103(a) as being obvious over as Van Rooijen et al. and Grøn et al., 1996, as applied to, at least, claims 1-3 and 5 above, in view of Grøn et al., 1992, of record.

Claim 49 is now included in the rejection of record in view of Applicant's amendment clarifying the claim's recitation. Applicant states no argument in the Remarks filed 12 August 2008 that may particularly address the rejection of record of claims 4, 6, 15, 16, and now claim 49, herein. Teachings of Van Rooijen et al. and Grøn et al., 1996, discussed above, are taken as before and combined with the teaching of Grøn et al., 1992, that the commercially prominent subtilisins, BPN' and Savinase, share a highest binding affinity for phenylalanine at their S4 binding subsites, have broad specificity for any amino acid at their S3 binding subsites with preference for a positively-charged amino acid, share a highest binding affinity for alanine at their S2 subsites, and share highest binding affinities for phenylalanine and leucine at their S4 subsites. See Tables II and III and accompanying discussion spanning pages 6014-6016. It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a fusion polypeptide comprising a modified subtilisin BPN' prodomain, e.g., modifying the native subtilisin BPN' prodomain set forth in SEQ ID NO:1 herein, to comprise, at least, the FKAF-modified prodomain according to claims 4, 6, 15, and 49 and further comprising a fusion partner of claim 16 that is a hormone of Van Rooijen et al., by preparing polynucleotides

encoding a fusion polypeptide comprising a modified subtilisin prodomain wherein the modified prodomains have enhanced affinity for binding to, and hydrolytic cleavage by, either a native subtilisin or modified subtilisin, and wherein the modifications comprise a phenylalanine at the P4 position, a charged amino acid, such as lysine, at the P3 position, an alanine at the P2 position and either a phenylalanine and leucine at the P1 position. This is because Grøn et al. 1992 teach that these are the kinds of amino acids having the highest binding affinities for the corresponding S1 through S4 subsites of the two most commonly-used subtilisins in the prior art. Based upon the teachings of the cited references, the level of skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success in practicing the claimed invention. The rejection of record, extended to claim 49, is therefore sustained.

Conclusion

The subject matters of a modified subtilisin prodomain comprising the tetrapeptide of claim 9, or a carboxyl-terminal nonapeptide having any of the six modifications represented by SEQ ID NO:7 herein of claim 10, remain free of the prior art of record herein. These claims are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action, accordingly, THIS ACTION IS **MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Jon Weber, Ph.D., can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or

relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

/William W. Moore/
22 December 2008

/Rebecca E. Prouty/
Primary Examiner
Art Unit 1652